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SYSTEMATIC REVIEWS AND META-ANALYSES

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Ursodeoxycholic Acid and Diets Higher in Fat Prevent Gallbladder Stones During Weight Loss: A Meta-analysis of Randomized Controlled Trials

Caroline S. Stokes,[*] Lise Lotte Gluud,[‡] Markus Casper,[*] and Frank Lammert[*]

[*]Department of Medicine II, Saarland University Medical Center, Homburg, Germany; and [‡]Diabetes Research Division, Department of Medicine, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

This article has an accompanying continuing medical education activity on page e61. Learning Objectives—At the end of this activity, the successful learner will be able to recognize the role of ursodeoxycholic acid in preventing primary gallbladder stones from forming during weight loss.

BACKGROUND & AIMS: **The prevalence of gallstones is increasing in association with the obesity epidemic, but rapid weight loss also increases the risk of stone formation. We conducted a systematic review of the efficacy of strategies to prevent gallbladder stones in adults as they lose weight.**

METHODS: **Randomized controlled trials of nonsurgical strategies to prevent gallstones were identified by electronic and manual searches. Our final analysis included 13 trials, comprising 1836 participants undergoing weight loss through dieting (8 trials) or bariatric surgery (5 trials). The trials compared ursodeoxycholic acid (UDCA) or high-fat weight loss diets with control interventions. We performed random-effects meta-analyses and evaluated heterogeneity and bias with subgroup, sensitivity, regression, and sequential analysis.**

RESULTS: **UDCA reduced the risk of ultrasound-verified gallstones compared with control interventions (risk ratio, 0.33; 95% confidence interval [CI], 0.18–0.60; number needed to treat, 9). This effect was significantly larger in trials of diets alone (risk ratio, 0.17; 95% CI, 0.11–0.25) than in trials of patients who underwent bariatric surgery (risk ratio, 0.42; 95% CI, 0.21–0.83) (test for subgroup differences, $P = .03$). UDCA reduced the risk of cholecystectomy for symptomatic stones (risk ratio, 0.20; 95% CI, 0.07–0.53). Diets high in fat content also reduced gallstones, compared with those with low fat content (risk ratio, 0.09; 95% CI, 0.01–0.61). The meta-analyses were confirmed in trials with a low risk of bias but not in sequential analysis. No additional beneficial or harmful outcomes were identified.**

CONCLUSIONS: **On the basis of a meta-analysis of randomized controlled trials, during weight loss, UDCA and/or higher dietary fat content appear to prevent formation of gallstones.**

Keywords: Bariatric Surgery; Cholelithiasis; Cholesterol; Obesity.

The prevalence of gallstones is currently between 10% and 20% in Western adults, with a projected rise because of the obesity epidemic and increase in metabolic syndrome and aging population.[1–3] An estimated 25% of gallstone carriers develop symptoms and complications such as cholecystitis, cholangitis, and pancreatitis.[4] Patients with symptomatic gallstones frequently require hospital admission and laparoscopic cholecystectomy. Annually more than 700,000 cholecystectomies are performed in the United States, which are not only associated with specific complications such as bile duct injury but also fatty liver disease[5] and represent a major economic burden on healthcare resources.[6]

Gallbladder stones comprise the common cholesterol stones and black pigment stones.[7] Currently more than 30% of Americans are obese,[8] and in particular, abdominal obesity is an established risk factor for cholesterol stones, because it promotes insulin resistance and biliary cholesterol hypersecretion.[9,10] A study in more than 90,000 women reported a 7-fold risk of gallstones in morbidly obese compared with normal weight populations.[11] However, cholesterol stones also frequently

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; CSI, cholesterol saturation index; LCD, low calorie diet; NNT, number needed to treat; RCT, randomized controlled trial; RR, risk ratio; UDCA, ursodeoxycholic acid; VLCD, very low calorie diet; WMD, weighed mean difference.**

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occur after rapid weight loss as a result of gallbladder hypomotility, and cholesterol supersaturation of bile as a result of reduced biliary bile salt secretion and enhanced mobilization of cholesterol.[12–15] During weight-reduction dieting, gallstones may develop after just 4 weeks.[15] Currently, no consensus exists with regard to gallstone prevention in obese patients undergoing weight reduction by bariatric surgery. Prophylactic cholecystectomy is often proposed for these individuals,[16] although the risk of developing symptomatic gallstones might be moderate.[17] However, obese patients undergoing gastric bypass surgery with concomitant cholecystectomy not only have a risk of postoperative complications but often require longer hospital stays.[18,19]

Lifestyle interventions such as physical activity or dietary fat manipulation during dieting have been investigated for gallstone prevention because of their capacity to promote gallbladder motility.[20] Clinical studies with bile acids, in particular ursodeoxycholic acid (UDCA), have demonstrated a decrease of bile lithogenicity through reducing the intestinal absorption and biliary secretion of cholesterol as well as shifting the phase separation of bile toward solubilization in micelles and vesicles.[21,22] A seminal randomized controlled trial[23] (RCT) in only 68 obese patients reported a reduced risk of gallstone formation with UDCA administration during weight loss on a very low calorie diet (VLCD). This finding was corroborated in further RCTs,[24,25] although others found no effect of UDCA on gallstone prevention during weight loss.[26,27] A meta-analysis of 5 RCTs after bariatric surgery reported a protective effect of UDCA against gallstones during weight loss[28] but did not evaluate trials using diet alone, and it did not assess for differences in weight loss after dieting only compared with surgery.

Nonsurgical preventions for primary gallstones need greater consideration, particularly because the American Medical Association recently declared that obesity should be categorized as a disease, requiring medical prevention and treatment.[29] Therefore, an increase in individuals at risk for gallbladder stones is to be expected. Because most RCTs with nonsurgical interventions include few patients and their combined effect is unclear, we conducted a systematic review and meta-analysis of RCTs to investigate the efficacy of nonsurgical preventive options for gallbladder stones in adults during weight loss after bariatric surgery or with diet alone.

Methods

The systematic review and meta-analyses were performed according to a published protocol[30] and followed the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions*.[31,32] The main objective was to evaluate the nonsurgical primary prevention of gallbladder stones, focusing on trials in patients undergoing intended weight loss. Our primary outcome measures were formation of ultrasonically verified gallstones, mortality, and adverse events. Secondary outcome measures included quality of life, cholecystectomy, bile lithogenicity (defined as changes in physiological parameters of bile composition indicative of an increased risk of gallstones, eg, cholesterol saturation index [CSI],[33] nucleation time for cholesterol crystal formation,[34] or presence of cholesterol crystals) and weight loss (reduction in body weight assessed in kilograms or by using the body mass index [BMI]). Interventions were included irrespective of the dose or class of drug. The control groups included placebo, no intervention, or pharmacologic and non-pharmacologic interventions. The threshold for duration of therapy was set to a minimum of 4 weeks.[15,35] Quasi-randomized trials and observational studies were only eligible for inclusion in the analyses of adverse events.

Search Strategy for Identification of Trials

We identified eligible RCTs through electronic and manual searches. Male and female adults (older than 18 years of age) were included irrespective of ethnicity. Participants were eligible for inclusion if they did not have gallbladder stones at baseline verified by ultrasonography. We searched the Cochrane Hepato-Biliary Group Controlled Trials Register,[32] the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded. The search was performed in each database from time of inception until July 2013 (Supplementary Table 1).

Trial registries were scanned in 2 search portals, the U.S. National Institutes of Health (www.clinicaltrials.gov) and the World Health Organization International Clinical Trial Registry Platform (www.who.int/ictrp/search/en/). We originally planned to include unpublished trials, but no such trial was identified. The manual search comprised scanning reference lists of relevant articles.

All references identified in the searches were reviewed, and potentially eligible trials were listed and compared against the inclusion criteria. Excluded trials were listed with the reason for exclusion. All authors agreed on the final inclusion of trials. Three authors extracted data independently by using standardized forms (M.C., L.G., and C.S.) and resolved disagreements through discussion. Authors of individual trials were contacted for any unclear or missing information. Two trials were translated into English before the data extraction.

Assessment of Bias

Trials were assessed by using the Cochrane Collaboration risk of bias tool.[31] Information was extracted for each trial by at least 2 authors, and risk of bias was rated as low or high (unlikely or likely to significantly influence the results) or unclear with regard to the following